Perfusion Weighted Imaging in body MRI

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Abstract

Dynamic contrast enhanced MRI (DCE-MRI) using small molecular weight gadolinium chelates enables non-invasive imaging characterization of tissue vascularity. Depending on the technique used, data reflecting tissue perfusion (blood flow, blood volume, mean transit time), microvessel permeability surface area product and extracellular leakage space can be obtained. Insights into these physiological processes can be obtained from inspection of kinetic enhancement curves or by the application of complex compartmental modeling techniques. Combining morphological and kinetic features can increase the accuracy of clinical diagnoses. Potential clinical applications include screening for malignant disease, lesion characterisation, monitoring lesion response to treatment and assessment of residual disease. Newer applications include prognostication, pharmacodynamic assessments of antivascular anticancer drugs and predicting efficacy of treatment.

Imaging tissue vascularity with MR Imaging

MRI techniques with contrast media are divided by the type of contrast medium used; (i) low molecular weight agents (<1kDa Daltons) that rapidly diffuse in the extracellular fluid space (ECF agents), (ii) intermediate molecular weight contrast agents and, (iii) large-molecular agents (>30 kDa Daltons) designed for prolonged intravascular retention (macromolecular contrast media, MMCM, or blood pool agents) (1) and (iii) agents intended to accumulate at sites of concentrated angiogenesis mediating molecules (2). This talk concentrates exclusively on non-invasive characterisation of vasculature with dynamic contrast medium enhanced MRI (DCE-MRI) using low-molecular weight contrast agents and explains how perfusion related data can be extracted depending on the technique utilized (3-6).

MRI Contrast agent kinetics

When a bolus of paramagnetic, low molecular weight contrast agent passes through a capillary bed, it is transiently confined within the vascular space. Concentrated contrast media within the vessels and in the immediate vicinity cause magnetic field (B_o) inhomogeneities that result in a decrease in the signal intensity of surrounding tissues (susceptibility effects). In most tissues except the brain, testes and retina, the contrast agent rapidly passes into the extravascular-extracellular space (EES, also called leakage space - v_e) at a rate determined by blood flow (which determines contrast medium delivery), the permeability and surface area of the microvessels. When low molecular weight contrast agents are used, typically 12-45% of the contrast media leaks into the EES during the first pass in tumours (7). The transfer constant (K^{trans}) describes the transendothelial transport of the contrast medium. Three major factors determine the behaviour of the contrast media during the first few minutes after injection; contrast medium delivery by blood perfusion, transport of contrast agent across vessel walls and diffusion of contrast medium in the interstitial space. If the delivery of the contrast medium to a tissue is insufficient with respect to maintaining a high enough concentration to continually supply the extracellular space (flow-limited situations or where vascular permeability is greater than inflow) then perfusion will determining contrast agent distribution and K^{trans} approximates to tissue blood flow per unit volume (8), this is a situation commonly found in tumours and in many normal tissue. If transport out of the vasculature does not deplete intravascular contrast medium concentration (non-flow limited situations) then K^{trans} approximates to permeability surface area product - PS. The latter circumstance occurs in some tumours that have a low blood supply such as lobular carcinoma, carcinoma in situ, in some brain tumour (which have a largely intact blood brain barrier) but can also occur in extracranial tumours usually after treatment (including chemotherapy and radiation), in fibrotic lesions and in some normal tissues.

As low molecular weight contrast media do not cross cell membranes, the volume of distribution is effectively the EES (v_e). After a variable time, the contrast agent diffuses back into the vasculature (described by the rate constant or k_{ep}) from where it is excreted principally by the kidneys although

some contrast media have significant hepatic excretion. When capillary permeability is very high, the return of contrast medium is typically rapid resulting in faster washout as plasma contrast agent concentrations fall. Contrast medium elimination from very slow-exchange tissues such as fibrosis and necrosis occurs more slowly and may occasionally be retained for a day or two.

MRI sequences can be designed to be sensitive to the vascular phase of contrast medium delivery (so-called T_2* or susceptibility based methods) which reflect on tissue perfusion and blood volume) (9, 10). T_1-weighted sequences are sensitive to the presence of diluted contrast medium in the EES and thus reflect microvessel perfusion, permeability and extracellular leakage space volume (so-called T_1 or relaxivity based methods). These two methods are compared in the Table.

Comparison of dynamic-MRI with functional-MDCT

	Dynamic susceptibility contrast enhanced MRI (DSC-MRI)	**Dynamic relaxivity contrast enhanced MRI (DCE-MRI)**
Mechanism of tissue enhancement	Susceptibility effects of contrast agent on magnetic field	Relaxivity effects of contrast agent on tissue water
Tissue compartment being interrogated	Vascular space	Vascular and extravascular space
Tissue signal intensity change	Darkening	Enhancement
Duration of effect and optimal data acquisition	Seconds / every 1-2 seconds	Minutes / 2-25 seconds
Magnitude of effect	Small	larger
SNR	Low	Very high
Quantification method used	Central volume theorem	General multi-compartment pharmacokinetic model
Kinetic parameters measured	Relative Blood Flow, Relative Blood Volume, Mean Transit Time	Transfer constants, leakage space, blood volume and flow

T_2*-weighted DSC-MRI (Dynamic susceptibility contrast enhanced MRI)

Data acquisition

Perfusion-weighted images can be obtained with "bolus-tracking techniques" that are sensitive to the passage of contrast material through a capillary bed (9, 10). A decrease in signal intensity of tissues caused by susceptibility occurs due to the presence of concentrated contrast media within vessels and in their immediate vicinity. The degree of observed signal intensity loss is dependent on the type of sequence used, on vascular concentration of the contrast agent and microvessel size (11) and density. The signal to noise ratio (SNR) of DSC-MR images can be enhanced by using higher doses of contrast medium (i.e., ≥0.2-mmol/kg body weight) (12).
The typical imaging strategy is to collect data using a fast imaging technique to produce a temporal resolution of approximately 2 seconds. During this short acquisition window it is usually possible to acquire multi-slice data at a matrix resolution of 128 x 128 or greater, depending on scanner specifications. High specification, echo-planar capable MRI systems allow 5-15 slices to be acquired. However, echo-planar sequences have limited applications in extracranial tissues due to greater intrinsic sensitivity to susceptibility-inducing environments (e.g., highly concentrated contrast media and bowel gas/tissue boundaries) which can result in spatial misregistration of major vessels during the first passage of the contrast agent thorough the vessels (13). Standard spoiled gradient-echo sequences on conventional MRI systems can also characterize these effects but are usually limited to a single slice. It has been noted that susceptibility-weighted spin-echo sequences are more sensitive to capillary blood flow and the signals obtained are of lower magnitude compared with gradient-echo sequences, which incorporate signals from larger vessels (14). It is unclear whether there are significant advantages of using spin-echo sequences but there are certainly significant costs in terms of signal to noise ratio.

Quantification

Analysis of DSC-MRI data is based on the assumption that the contrast agent remains within the vascular space throughout the examination acting as a blood pool marker. This assumption is untrue except in the brain where there is no contrast medium leakage due to the blood–brain barrier. The application of DSC-MRI was therefore initially limited to studies of normal brain although modifications of the technique have subsequently allowed its use in enhancing tissues (see below). The conventional approach to calculating blood flow uses the area under the contrast concentration curve as an estimate of blood volume within the pixel (BV) and the width of the contrast bolus as an estimate of the mean transit time (MTT). MTT is the average time the contrast agent takes to pass through the tissue being studied (9, 10, 15). Blood flow (BF) can be calculated by using the central volume theorem equation (BF = BV/MTT). The initial calculation of local contrast concentration from the observed signal change is straightforward as contrast concentration is linearly related to the T_2 rate changes (ΔR_2), which can be calculated for using the relationship

$\Delta R_2 = -\ln(S(t)/S(0))/TE$

where $S(0)$ is the base line signal intensity, $S(t)$ is the pixel intensity at time t and TE is the echo time. This allows transformation of signal intensity time course data to changing R_2.

The most robust parameter which can be extracted reliably from first pass techniques is BV, which is obtained from the integral of the data time series during the first pass of the contrast agent (16).

$$\mathrm{rCBV} = \int_{t_0}^{t_e} \Delta \mathrm{R2}(t)\mathrm{d}t \qquad (3)$$

where t_0 is the time of first arrival of contrast and t_e is the time at which ΔR_2 returns to baseline values. The MTT is then estimated from the width of the curve such as at the width at half the maximum height (full width at half maximum; FWHM).

In addition to the flow related parameters described above, it is also possible calculate time to contrast medium arrival into a tissue (T_0) or, more commonly the time to peak concentration (TTP). Additionally, an appreciation of the spatial distribution of tissue perfusion can be obtained by simple subtraction images taken at the nadir point (maximal signal attenuation). This simply obtained image has been strongly correlated with relative blood flow and volume in tumours (34, 35). Subtraction analysis should only be done if the is a linear relationship between rBV and rBF; that is, when mean transit time (MTT) is in a narrow range. The correlation between the maximum signal intensity drop and rBV/rBF appears good in untreated tumours but this relationship does not appear to be sustained following therapy (17). Absolute quantification of DSC-MRI parameters can be obtained by measuring the changing concentration of contrast agent in the feeding vessel, and in this way, quantified perfusion parameters in normal brain and of low grade gliomas have been obtained (19, 20). Absolute quantification is not currently possible for evaluation of visceral tissues and tumours due to a number of limitations that are discussed below.

Limitations

There are a number of limitations of DSC-MRI techniques which include the effects of contrast medium recirculation, contrast medium leakage and subsequent tissue enhancement and bolus dispersion (3).

Analysis of the contrast bolus passage assumes that the bolus passes through the tissue and that the signal intensity (i.e., concentration of contrast medium) then returns to zero. In practice, the contrast medium re-circulates through the body and a second re-circulation peak is always seen. With bolus dispersion the second peak is lower and broader than the first pass and by the time of the third re-circulation the intravascular contrast has mixed evenly throughout the blood volume. Measurement of kinetic parameters is therefore subject to errors due to the presence of both first pass and re-circulating contrast in the vessels during the later part of the bolus passage. One way or overcoming this limitation is to use an idealized model to the observed data. This relies on the fact that the shape of the contrast concentration curve during the passage of the first bolus can be shown theoretically to

always conform to a specific shape known as a gamma variate (21). The use of curve fitting also smoothes the data, effectively reducing noise and eliminates the contamination of the first pass bolus due to contrast agent re-circulation.

Loss of contrast medium compartmentalization during the first pass into the interstitial space will cause aberrant signal intensity changes by the end of the experiment (either enhancement or failure of the signal intensity to return to baseline). Recirculation and contrast leakage into the extracellular space during the first pass of contrast medium are the principle causes of falsely lower blood volume values. Furthermore, the T_1 signal enhancing effects of contrast medium leaking from blood vessels can counteract T_2* signal lowering effects. Quantitative imaging is thus most reliably used for normal brain and non-enhancing brain lesions because the contrast medium is completely or largely retained within the intravascular space.

Solutions for counteracting the T_1 enhancing effects of gadolinium chelates include optimization of sequences, by using dual or multi-echo sequences that minimize T_1 sensitivity (22) and pre-dosing with contrast medium to saturate the leakage space. (1) The use of techniques with reduced T_1 sensitivity, such as low flip angle gradient-echo based sequences, effectively removes relaxivity effects although some workers have observed residual effects in rapidly enhancing tumours (23, 24). The major problem with this method is the lowering of signal to noise ratio produced by the reduction in flip angle although this can be partially compensated by increasing contrast agent doses. (2) Another approach to reducing T_1 sensitivity is to use a dual echo technique in which the T_1 weighted first echo is used to correct the predominantly T_2 weighted second echo (25) (22). The dual echo technique is technically challenging for most machines and reducing sampling time inevitably restricts the number of samples and therefore slices which can be obtained. (3) the third approach is to use pre-enhancement with an additional dose of contrast agent. Saturating the extracellular with contrast medium induces maximum T_1 shortening and the arrival of further contrast medium given during the susceptibility experiment causes little additional relaxivity based signal intensity responses. Recently, Johnson et al, have shown that it is possible to pharmacokinetically model the first pass effect in the presence of leaking capillaries and to obtain an estimate of blood volume, vascular transfer constant, and EES volume (26). Other solutions for overcoming some of these problems include the use of non-gadolinium susceptibility contrast agents based on the element dysprosium or ultrasmall superparamagnetic iron oxide particles (USPIOs), which have strong T_2* effects but weak T_1 effects (27, 28). Preliminary results have indicated that dysprosium-based relative cerebral blood volume (rCBV) maps are superior to those obtained with gadolinium chelates (29, 30). USPIOs designed for bolus injection have the advantage of being retained within the vascular space during the first pass due to their larger size (31, 32).

As noted above, the measurement of CBF requires an accurate estimation of MTT which is extracted from the width of the contrast bolus. The width of the contrast bolus is actually affected by a combination of three factors. These are: 1) the width of the bolus at the tissue level (the arterial input function or AIF); 2) changes in bolus width due to regional alterations in flow related to non-laminar flow (which arises from the presence of irregular caliber vessels), non-dichotomous branching and high vascular permeability (which leads to increased blood viscosity from haemoconcentration) and variations in the haematocrit fraction as blood passes through a vascular bed; and 3) physical bolus broadening due to dispersive effects which are unrelated to flow. Additionally, the width of the bolus is strongly affected by individual variations in injection technique, contrast dose and cardiovascular functioning and structural architecture including upstream vascular stenoses.

Clinical experience

Quantitative imaging is currently most reliable for normal brain and non-enhancing brain lesions because the contrast medium is retained within the intravascular space. T_2*-weighted perfusion mapping techniques have progressively entered neurological practice (33-35). Clinical applications include characterisation of tumour vascularity (23, 36-38), follow-up of treatment response (20, 33, 35, 39) and the study of stroke (40). There is very little literature data on T_2* weighted DCE-MRI outside the brain. Both Kuhl et al. and Kvistad et al. have qualitatively evaluated the value of T_2*-weighted DCE-MRI for characterizing breast lesions (41, 42). Both studies showed strong decreases in signal intensity in malignant tissues whereas susceptibility effects in fibroadenomas were minor. Quantitative T_2*-weighted DCE-MRI have been used to monitor the effects of chemotherapy in breast cancer. Ah-See et al. have observed that rBV and rBF reduce with successful treatment whereas no changes were seen in non-responding tumours (43).

T_1-weighted DCE-MRI (Dynamic relaxivity enhanced MRI)

Data acquisition

Extracellular contrast media readily diffuse from the blood into the EES of tissues at a rate determined by tissue perfusion, permeability of the capillaries and their surface area. Increases in T_1 relaxation rate caused by the contrast medium is the mechanism of tissue enhancement. Most DCE-MRI studies employ 2D/3D T_1-weighted gradient-echo, saturation recovery/inversion recovery snapshot sequences (e.g., turboFLASH) or echoplanar sequences. Each of these techniques enable tissue T_1 relaxation rates to be estimated in a reasonably short period of time and this allows quantification of tissue contrast medium concentration (44-48). The choice of sequence and parameters used is dependent on intrinsic advantages and disadvantages of the sequences taking into account T_1 sensitivity, anatomical coverage, acquisition times, susceptibility to artefacts arising from magnetic field inhomogeneities and accuracy for quantification. The amount of signal enhancement observed on T_1-weighted images is dependent on a number of physiological and physical factors. Physiological factors include tissue perfusion, capillary surface area, permeability to contrast agent and volume of the extracellular leakage space. Physical factors include the native (or pre-contrast) T_1-relaxation rate of the tissue, contrast agent dose, rate of intracellular-extracellular water exchange, imaging sequence parameters used and on measurement gain and scaling factors. T_1-weighted kinetic enhancement curves have 3 distinct phases; the upslope, maximum enhancement and washout. It is generally recognised that the upslope is highly dependent on tissue perfusion and permeability with perfusion predominating. Maximum enhancement is related to the total uptake concentration of the contrast medium in the interstitial space (with an additional vascular contribution) and washout rate is associated with tissue contrast agent concentration decrease and thus is strongly related to vascular permeability. If it is assumed that tissue enhancement has contributions from vascular and extravascular compartments (see two-compartment modelling below) then it is possible to separate these inputs mathematically using deconvolution techniques (49) which is helpful for understanding the shape of kinetic curves (50). The dominant contribution of perfusion to the upslope of T_1-weighted DCE-MRI enhancement curves can be verified empirically by correlating T_1- and T_2*-weighted DCE-MRI enhancement curves and corresponding kinetic pixel maps (22).

Quantification

Signal enhancement seen on T_1-weighted DCE-MRI can be assessed in two ways: by the analysis of signal intensity changes (semi-quantitative) and/or by quantifying tissue T_1 relativity (R_1) or contrast agent concentration change using pharmacokinetic modelling techniques. Semi-quantitative parameters describe signal intensity changes using a number of descriptors. These parameters include curve shape classification done visually (51, 52), onset time (a number of definitions exist), gradient of the upslope of enhancement curves, maximum signal intensity and washout gradient (combinations of these can also be found in the literature). As the rate of enhancement has been shown to be important for improving the specificity of clinical diagnoses, parameters that include a timing element are often used (e.g., maximum intensity time ratio (MITR) (53) and maximum focal enhancement at one minute (54, 55). The uptake integral or initial area under the signal intensity (IAUC) or gadolinium contrast medium concentration (IAUGC) curve has been also been studied (56). IAUGC is a relatively robust and simple technique, which characterizes all enhancing regions without the problems associated with model fitting failures in pharmacokinetic models (see below). However, IAUGC does not have a simple relationship to the physiology parameters of interest (perfusion, permeability and leakage space). Thus, semi-quantitative parameters have a close but complex and not well defined link to underlying tissue physiology but have the advantage of being relatively straightforward to calculate. Limitations of semi-quantitative parameters include the fact that they are derived from signal intensity data that may not accurately reflect the changing contrast medium concentration in tissues and that signal intensity data can be influenced by scanner settings (including gain and scaling factors). These factors limit the usefulness of semi-quantitative parameters and make between-patient and between-system comparisons potentially problematic.

Quantitative techniques use pharmacokinetic modelling applied to changes in tissue contrast agent concentration or R_1. In general, it is not recommended that pharmacokinetic modelling be done on signal intensity data unless it is has been shown that there is a direct relationship between signal intensity and contrast agent concentration over the entire range expected in tissues. Signal intensity changes observed during dynamic acquisition are used to estimate contrast agent concentration *in*

vivo (44, 45, 48, 57). Concentration-time curves are then mathematically fitted using one of a number of recognised pharmacokinetic models principally those of Larsson, Tofts and Kermode (58, 59).

Kinetic modeling

As low molecular weight contrast agents exchange between central and the extra-cellular space of tumours so the pharmacokinetic models used consist of two compartments: the central blood plasma compartment and the tissue extra-cellular compartment. The rate equation describing the transport of the contrast agent between the compartments is the following: (8, 60, 61)

$$\frac{dC_t(t)}{dt} = K^{trans} C_p(t) - k_{ep} C_t(t)$$

Where Ct(t) is the tissue concentration, Cp(t) is the plasma concentration, K^{trans} and k_{ep} are volume rate constants for exchange between central and tissue compartments and vice versa respectively reflecting bulk tissue properties. Again following Tofts et al 1999 (8) the extra-cellular extra vascular space (v_e) is defined as

$$v_e = \frac{K^{trans}}{K_{ep}}$$

K^{trans} is considered within a general mixed perfusion and permeability condition to be equal to E*F*rho(1-Hct), where E is the extraction fraction of the contrast tracer, F is blood flow, rho is tissue density and Hct is the haematocrit. As already noted in the section on contrast agent kinetics, when flow is adequate and the rate of extraction E is small compared to supply, then K^{trans} is largely equal to the product of the capillary permeability and surface area. If the delivery of the contrast agent to tissue is insufficient then blood perfusion is the dominant factor. However, it should be noted that in tissue regions with poor blood supply low K^{trans} values can be obtained in regions where there would otherwise be high vessel permeability (62).

A major difficulty for quantitative DCE-MRI is the determination of the Cp(t) required for model based analysis. Measuring Cp(t) (often called the arterial input function) directly using DCE-MRI requires measurement sequences, which yield signal intensity outputs that scale linearly over a large range of tissue and plasma concentrations. Cp(t) has to be sampled in an artery at sufficient temporal resolution to accurately characterise the rapidly changing in tracer concentration following a bolus injection (ideally less than <2 seconds), which is currently impractical within the constraints of useful spatial image resolution. Further confounding factors in measurements of Cp(t) are inflow artefacts and motion. There are also difficulties relating to water proton exchange kinetics within the blood plasma. It is generally assumed that gadolinium containing chelates interact sufficiently quickly with the plasma water protons to induce relaxation which directly proportional to chelates concentrations but this assumption ignores the rate of exchange of water protons between the intra and extracellular spaces in blood. It has been shown that substantial errors can occur when ignoring the effects of water exchange (63).

Several approaches have been utilized for obtaining or estimating Cp(t) with an acceptance of the limitations described. The most common method of obtaining Cp(t) is to use a general input function derived from real measurement of plasma concentration done in volunteers (64, 65). An alternative method is to use a reference tissue from which an estimate of Cp(t) can be derived from the Kety equation using the reference tissue concentration Ct(t) data and known physiological parameters of the reference tissue (66, 67). In practice a polynomial function is fitted the Ct(t) curve from which the required derivative is obtained. The advantages of the reference tissue approach are that the temporal sampling can be relaxed, as the rate of change in tracer concentration in the reference tissue is not as rapid as in plasma, the size of the reference tissue sample can be large which improves the signal to noise ratio of the Ct(t) obtained and averages motion effects, the effects of water exchange are minimised, as water proton are in fast exchange in tissue and the haematocrit fraction is smaller in reference tissue capillaries (e.g., muscle). The disadvantages are that clinical treatments, may effect blood flow in reference tissues and the implicit assumption that the reference tissue derived Cp(t) is relevant to the tissues of interest (i.e., the tumour).

As already noted, model based analysis of DCE-MRI data involves model fitting the individual pixel concentration time curves to a general solution to the Kety equation. If the plasma concentration Cp(t) is described as the sum of two decaying exponential (64) the following solution can be obtained

$$C_t(t) = D \cdot K^{trans} \cdot \sum_{i=1}^{2} a_i \cdot \frac{\left[e^{-\left(\frac{K^{trans}}{v_e} \right) \cdot (t - t_o)} - e^{-m_i \cdot (t - t_o)} \right]}{m_i - \left(\frac{K^{trans}}{v_e} \right)}$$

where D= dose of contrast medium, m_i are rate constants for elimination and a_i are physiologically derived constants. Using this equation it is possible to fit individual pixel derived time series data Ct(t). The results of the fitting process can be used to generate parametric images (K^{trans}, v_e, k_{ep}) and these parametric images can be overlaid onto the source anatomical images. The advantage of individual fitted pixels is that the parametric images provide an indication of the heterogeneity of the distributions of model-based parameters. There are a number of extensions to the basic model described above. One major assumption in the generalised model of Tofts is that the tissue vascular fraction (vp) is small and can be ignored, however in tumours this is not necessarily the case. A solution which includes the vp contribution (61) is widely used in radio-nuclear and computer tomography tracer kinetic studies and has been shown to be useful in DCE-MRI in so called first pass studies in which the model is applied only for the first pass of the tracer through the circulatory system (68). It is important when applying this model to avoid recirculation effects of the tracer and to obtain a sufficient number of sample points within the first pass; a temporal resolution in the order of 1 second is ideal. Rapid data acquisition with a temporal resolution of 1 second per image can be achieved with sophisticated DCE-MRI measurements using data sharing (22). A further advantage of the Patlak method is the ease of computation of the model parameters as the model solution can be linear, which is computationally efficient to solve. The 'Patlak' solution is;

$$C_t(t) = v_p \cdot C_p(t) + K^{trans} \cdot \int_0^t C_p(\tau)\, d\tau \qquad Y = \frac{C_t(t)}{C_p(t)} \qquad X = \frac{\int_0^\tau C_p(\tau)\, d\tau}{C_p(t)}$$

which is linearised by expressing the Patlak equation in terms of Y and X axes shown above. The Y intercept provides an estimate of vp and the slope is K^{trans}. A disadvantage of this approach is that it is not possible to estimate v_e. For further detailed discussion on pharmacokinetic modelling techniques readers are directed to the review by Tofts (69) and a detailed analysis of the data acquisition methodology can be found in the review Dale et al (70).

Limitations

Quantitative parameters are more complicated to derive compared with those derived semi-quantitatively which deters their use at the workbench. Difficulties arise from more complex data acquisition requirements and by the lack of commercially available software to analyze acquired data. The model chosen may not exactly fit the data obtained and each model makes a number of assumptions that may not be valid for every tissue or tumour type (8, 69). From the above discussions, it is clear that there are uncertainties with regard to the reliability of kinetic parameter estimates derived from the application of tracer kinetic models to T1-weighted DCE-MRI data (63, 71, 72). These derive from assumptions implicit in kinetic models and those for the measurement of tissue contrast agent concentration (70). For example, the Tofts' model uses a standard description of the time varying blood concentration of contrast agent (64), and assumes that the supply of contrast medium is not flow limited and that tissue blood volume contributes negligibly to signal intensity changes compared with that arising from contrast medium in the interstitial space. As already noted above, this is not universally true in extracranial tumours. Buckley has suggested that the application

of commonly accepted models and their respective model-based assumptions to DCE-MRI data leads to systematic overestimation of K^{trans} in tumours (73). Thus, it is difficult to be certain about how accurately model-based kinetic parameter estimates compare with the physiological parameter that they purport to measure, particularly as there is no reliable clinical gold standard.

Despite these complexities it is important to remember that quantitative kinetic parameters can provide insights into underlying tissue pathophysiological processes that semi-quantitative descriptors cannot. If the time varying contrast agent concentration can be measured accurately and the type, volume and method of administration of contrast agent are consistent, then it is possible to compare directly pharmacokinetic parameters acquired serially in a given patient and in different patients imaged at the same or different scanning sites. Furthermore, it is possible to use quantitative DCE-MRI as a tool for decision making as attested to by extensive clinical experience (see below).

Validation

Recently Kiessling et al. reported a strong positive correlation between microbubble enhanced Doppler ultrasound and dynamic T_1-weighted DCE-MRI kinetic parameters (74). Previously, it has been shown that there is a near-linear correlation between microbubble velocity measured on Doppler ultrasound and red blood cell velocity (75). Both Lankester et al. and Ah-See et al. have shown strong positive correlations between K^{trans} and relative blood flow (rBF) derived from T_1- and T_2*-weighted DCE-MRI in pelvic and breast cancer respectively (76)[Lankester K, personal communication] but such a correlation has not been observed for rectal cancers (77).
Many studies have attempted to correlate tissue MR enhancement with immuno-histochemical microvessel density (MVD) measurements in a variety of tumours. Some MRI studies have shown broad correlations between T_1 kinetic parameters estimates and MVD (74, 78-83) whereas others have found no correlation (50, 84, 85). Recently VEGF, a potent vascular permeability and angiogenic factor, has been implicated as an additional explanatory factor that determines MR signal enhancement. Knopp et al. reported that MRI vascular permeability to contrast media closely correlated with tissue VEGF expression in breast tumours (86) whereas Su et al. and Ah-See et al. did not (50, 87). The importance of the role of VEGF in determining MR enhancement is supported by the spatial association of hyperpermeable capillaries detected by macromolecular contrast enhanced MRI and VEGF expression on histological specimens (88). Furthermore, the observation that T_1-weighted DCE-MRI measurements can detect changes in flow and permeability after anti-VEGF antibody and the administration of inhibitors of VEGF signalling, in xenografts (89-92) and in humans (93-95) lends weight to the important role played by VEGF in determining MR enhancement. Other tissue characteristics that have been correlated with T_1-weighted enhancement patterns include the degree of stromal cellularity and fibrosis (96, 97), tissue oxygenation (85, 98) and tumour proliferation (80, 99).

Clinical experience

Analysis of enhancement seen on T_1-weighted DCE-MRI is a valuable diagnostic tool in a number of clinical situations. The most established role is in lesion characterisation where it has found a role in distinguishing benign from malignant breast and musculoskeletal lesions (51-55, 100). In the brain, T_1 DCE-MRI can be used to non-invasively grade brain tumors (101-103). Dynamic T_1-weighted MRI studies have also been found to be of value in staging gynaecological malignancies, bladder and prostate cancers (104-107). DCE-MRI studies have also been found to be of value in detecting tumour relapse in the presence of fibrosis within treated tissues of the breast and pelvis (108-115). DCE-MRI is also able to predict response to or monitor the effects of a variety of treatments. These include neoadjuvant chemotherapy in bladder and breast cancers and bone sarcomas (116-119). Other treatments that can be monitored include radiotherapy in rectal and cervix cancers (120-123) androgen deprivation in prostate cancer (124) and vascular embolisation of uterine fibroids (125-127). Recently, DCE-MRI has been used to monitor the effects of antivascular anticancer drugs (93-95, 128-130). It is noteworthy that enhancement on Dynamic T_1-weighted DCE-MRI can be affected by most types of successful treatments. This reflects on the fact that tumour cell kill, no matter how achieved, ultimately results in vascular shut down, probably because of the loss of proangiogenic cytokine support which results in apoptosis of proliferating endothelial cells.

Challenges for Perfusion DCE-MRI

For DCE-MRI it is recognized that **high-resolution and short imaging-time** are competing examination strategies on current equipment and software. Higher temporal resolution imaging necessitates reduced spatial resolution, decreased anatomic coverage or a combination of them.

Accuracy in the parameters derived from DCE-MRI, is dependent on the image acquisition rate as can be seen from the following expression $$E = \sqrt{\sum_{i=1}^{N} \frac{\left(C_i^2 - c_i^2\right)^2}{N - P}}$$ where E is the error, N the number of sample data points, P the number of free parameters in the model, C_i is the contrast media concentration and c_i is the model estimate of the contrast media concentration (131). From this expression we can immediately see that a small number of sample points N leads to large error estimates. High spatial resolution will by necessity reduce the number of data samples leading to increased error estimates. Additionally, the finer the spatial resolution the greater the need for accurate image registration as mis-registration will result in increased motion-induced noise in data. Conversely a large number of data samples acquired at a high sampling rate reduces the error and enables more complex models with a greater number of free variables to be used in the model fitting process. Thus compromises have to be made trading temporal resolution against coverage and spatial resolution. Even though data collection procedures for quantitative examinations differ to those used in routine clinical practice; there is debate as to which technique(s) is/are best (62, 132, 133). To meet this need, the MRI community has meet on a number of occasions and agreed examination and analysis protocols in order to enable DCE-MRI to be more completely validated and used in clinical trials. Both generic and organ-specific consensus methods for quantified T_1-weighted DCE-MRI data collection can now be found (134-137).

A major source of variability in the DCE-MRI literature relates to the method of **contrast administration**. The dose and method of administration of contrast agent affects modelling procedures and clinical results. Typically, contrast agents are given either as a bolus (58) or infusion (138). When a powered injector is used, reproducible injections are ensured. Short injection times are optimal for fast DCE-MRI imaging techniques especially when evaluating lesions with high microvessel permeability for ECF contrast agents (139, 140) but conversely, slower infusion methods may be better when the temporal resolution of the study is longer and volume coverage is being undertaken (132). The method of contrast medium administration also needs to be tailored to the sequence used and sequence sensitivity to T_2* and T_1 effects (141-143). Using injection rates of 5ml/s can reduce the T_1 and T_2 relaxation times in blood to the order of 10ms during the first pass of the contrast medium (144). Gradient echo sequences using echo times of the order of 10ms will be subject to significant T_2 related attenuation that will require correction in quantitative analysis methods. The current trend in DCE-MRI is to acquire data in 3D volumes; this requires the use of both short repetition times (TR) and short echo times (TE). The short TR requires that DCE-MRI data are acquired with a small nutation angles for excitation. This is for two reasons; to reduce the specific absorption rate of electromagnetic energy in the body (a safety reason) and to ensure that the signal obtained is related to the actual concentration of contrast medium. A consequence of this is that a number of pre-contrast measurements with differing nutation angles are required to obtain sufficient data for the calculation of the initial tissue relaxation rate (R_1). However, larger nutation angles also reduce the signal to noise ratio of the measurement which can be compensated for in part by the SNR advantage of obtaining 3D volumes.

Another issue that needs to be addressed is that of data collection in body parts where there is a large degree of **physiological movement** such as the lungs and liver. The presence of motion can invalidate functional vascular parameter estimates particularly for pixel-by-pixel analyses. Methods for overcoming/minimizing these effects include the application of navigator techniques (145) or imaging in the non-axial plane using sequential breath-holds during data acquisition and subsequently registering the data prior to analysis (146). Unlike navigator techniques, the latter method has the advantage that a fixed time interval between measurements is maintained. Sophisticated image registration methods have also been used to eliminate mis-registration and motion induced noise in DCE-MRI studies in breast (147).

A practical question often asked is whether it is necessary to quantify imaging data to answer important clinical questions. Simple morphologic and semi-quantitative analyses seem to work well in the clinic. However, it is important to realize that semi-quantitative diagnostic criteria cannot be applied simply from one centre to another particularly, when different equipment and sequences are used. **Quantification techniques** aim to minimize errors that can result from the use of different equipment and imaging protocols. Quantification techniques also enable the derivation of kinetic

parameters that are based on some understanding of physiological processes and so can provide insights into tumour biology (see above). Quantification techniques are therefore preferred when evaluating antivascular anticancer drugs (148). Quantification techniques rely on the fitting of the data acquired to a mathematical model. Experience shows that the model chosen may not fit the data acquired (modelling failures) and that apparently sensible kinetic values can be obtained even from noisy data. The causes of modelling failures are complex and often not well understood. Reasons include high vascular permeability (i.e. when the intravascular contrast medium concentration cannot be maintained due to markedly leaky vessels in the setting of limited blood flow), high tissue blood volumes, multiple tissue compartments and an incorrect or assumed **arterial input function** (some organs (liver and lung) and tumours have a dual blood supply (both arterial and venous) complicating modelling procedures). Modelling failures would be reduced if the arterial input function (AIF) was measured and used to estimate kinetic parameters. Fitting data with the Tofts' model can be improved if patient derived vascular input functions are used as inputs in the pharmacokinetic model in place of the standard Weinmann coefficients (64). Reliable methods for measuring arterial input functions for routine DCE-MRI studies are now emerging (66-68, 149, 150). The use of IAUC for both T_1 and T_2* data overcomes the issue of characterizing pixels which fail to fit a model, a major problem found in pharmacokinetic model based approaches.

Inevitably the future will yield **kinetic models of increasing sophistication** - for example, the effects of variable proton exchange rates are yet to be incorporated into a model of contrast agent uptake. We do not have models that fit all data types and more sophisticated models that provide insights into tissue compartment behaviour are needed (8, 141). It is probably true that modelling approaches are not always applied to suitable data in ways that are robust to over-fitting, systematic errors, and noise. The application of more sophisticated models available in the literature requires superior scanning methods to achieve their full potential. The combination of 3 Tesla scanning and parallel imaging techniques will allow very rapid data acquisition of suitable signal-to-noise ratio to allow increased accuracy and precision in quantitative DCE-MRI.

Analysis and presentation of imaging data needs to take into account the **heterogeneity** of tumour vascular characteristics. User-defined whole tumour regions of interest (ROI) yield graphical outputs with good signal-to-noise ratio, but lack spatial resolution and are prone to partial volume averaging errors and thus are unable to evaluate tumour heterogeneity. As a result, whole tumour ROIs may not reflect small areas of rapid change and so may be insensitive to drug action. Many authors have commented that whole tumour ROI assessment may be inappropriate particularly for the evaluation of malignant lesions where heterogeneous areas of enhancement are diagnostically important (23, 48, 55). Pixel mapping has a number of advantages including the appreciation of heterogeneity of enhancement and removal for the need to selectively place user-defined ROIs. The risk of missing important diagnostic information and of creating ROIs that contain more than one tissue type is reduced. An important advantage of pixel mapping is being able to spatially map tumour vascular characteristics such as blood volume, blood flow, permeability and leakage space in a single patient and to be able to probe the relationship between different kinetic parameters. Such displays provide unique insights into tumour structure, function and response to treatment. Pixel mapping techniques have the disadvantages of having poor signal-to-noise ratios and require specialist software for their generation. Whilst visual appreciation of heterogeneity is improved by pixel mapping displays, quantification of the same can be more difficult. Recently, histogram and principal components analysis and fractal approaches have been used to quantify the heterogeneity of tumours for comparative and longitudinal studies, for monitoring the effects of treatment and to show the regression or development of angiogenic hot spots (122, 151-153).

Conclusions

There are definite clinical requirements to develop non-invasive imaging assays of tumor microcirculation. DCE-MRI is the favored technique for evaluating tumors with respect to their state of the functional microcirculation. Depending on the technique used, data reflecting tissue perfusion (blood flow, blood volume, mean transit time), microvessel permeability surface area product and extracellular leakage space can be obtained. Insights into these physiological processes can be obtained from inspection of kinetic enhancement curves or by the application of complex compartmental modeling techniques. The accuracy of clinical diagnoses can be increased by combining morphological and kinetic features. Angiogenesis imaging techniques potentially have widespread clinical applications and their recent development has been spurred on by the development of antivascular anticancer approaches. A realistic appraisal of the strengths and

limitations of techniques is required and a number of challenges must be met if they are to enter into widespread clinical practice. Such developments will be essential for multicentre trials where it will be necessary to establish effective cross-site standardization of measurements and evaluation.

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